Chapter I

HISTORICAL INTRODUCTION TO THE PROBLEM OF DIFFERENTIATION

§ 1

The production of the adult living organism with all its complexity out of a simple egg (or its equivalent in the terminology of the ancients) is a phenomenon and a problem which has attracted the attention of philosophers as well as of scientists for over two thousand years. To give a brief account of the history of ideas relating to this problem is no easy matter, but the task is fortunately facilitated by the fact that Dr E. S. Russell and Prof. F. J. Cole, F.R.S. have recently devoted volumes to certain aspects of this subject, and to the reader who desires to become better acquainted with it, no better advice can be given than to refer him to *The Interpretation of Development and Heredity*, and to *Early Theories of Sexual Generation*. The historical section of Dr Needham's *Chemical Embryology*, and various works of Dr Charles Singer also provide much valuable information.

Meanwhile, a brief attempt will be made in the following few pages to outline the essential features of the chief schools of thought concerning problems of development, in order to show how the modern science of experimental embryology came into being, and to present it in its proper historical setting.

The kernel of the problem is the appearance during individual development of complexity of form and of function where previously no such complexity existed. In the past, there have existed two sharply contrasted sets of theories to account for it. One view accepts the phenomenon as essentially a genesis of diversity, a new creation, and attempts to understand it as such. This coming into existence of new complexity of form and function during development is styled *epigenesis*.

The difficulties which other thinkers experienced in trying to understand how epigenesis may be brought about led them to deny that it exists: i.e. to say that there is no fresh creation of diversity in development from the egg, but only a realisation, expansion, and rendering visible of a pre-existing diversity. *Preformation* is the fundamental assumption of views of this type, and they are classed together as preformationist theories. But the doctrine of preformation, however, met with even graver obstacles, both logical and empirical, than the opposite view, and biological opinion is now united in maintaining the existence of a true epigenesis in development. In recent years, however, the discoveries of genetics have reintroduced certain elements of the preformationist theory, but in more subtle form. As will be seen later, the modern view is rigorously preformationist as regards the hereditary constitution of an organism, but rigorously epigenetic as regards its embryological development.

To a large extent, the preformationist view assumes as already given that which the epigenetic attempts to study and to explain; and the problem is complicated by the fact that notions of embryonic development have been confused with concepts of heredity. This is evident in the attempt, on the part of the author of *Peri Gones* in the Hippocratic corpus, to explain development by assuming a part-to-part correspondence between the parts of the body of the parent and those of the offspring: the corresponding parts being related to one another via the "semen", or, as would now be said, via the germ-cells. By assuming that the embryo at its earliest stage is a minute replica of the adult, its parts having been "preformed" by representative particles coming from the corresponding parts of the parent, the preformationist hypothesis attempts to solve at one stroke both the problem of hereditary resemblance between generations and the problem of development within each generation.

This view was in reality shattered by Aristotle's criticism, but it was revived and widely held during the seventeenth and eighteenth centuries, largely owing to the fact that mechanistic explanations had come into vogue, and it seemed impossible to understand epigenesis on mechanistic lines. One of the foremost exponents of the preformationist hypothesis was Charles Bonnet. His views were freed from the crude idea that the preformation in the egg was spatially identical with the arrangement of parts in the adult and fully developed animal, or that the "homunculus" in the sperm, with the head, trunk, arms and legs which it was supposed to have (and which certain over-enthusiastic observers claimed to have seen through their microscopes; see Cole's *Early Theories of Sexual Generation*) only required to increase in size, as if inflated by a pump, in order to produce development. Instead of regarding the rudiments of the organs as being preformed in their definitive adult positions, Bonnet imagined them as "organic points" which subsequently had to undergo considerable translocation and rearrangement. He was thus able to reconcile his belief in preformation with the empirical fact that the germ or blastoderm of the early chick showed no resemblance to a hen.

Bonnet's theories were ahead of his facts, and, indeed, he seems to have been proud of it, for he refers to the preformationist view as "the most striking victory of reason over the senses". The hypothesis of such an invisible and elastic preformation was perhaps permissible in Bonnet's day, but later observational and experimental evidence has rendered it utterly untenable. Further, a rigid preformationist view which asserts that the egg is a miniature and preformed adult, necessarily implies that the egg must also contain the eggs for the next generation; the latter eggs must therefore also contain miniature embryos and the eggs for their subsequent generations. Bonnet realised that an *emboîtement* or encasement of this kind *ad infinitum* would be an absurdity. (Incidentally, it may be noticed that if it were true, phylogenetic evolution—unless it too were preformed and predetermined—would be an impossibility.) But then, if *all* subsequent generations are not preformed in miniature now, there must come a time when they *are* determined and preformed. Before this time they were neither determined nor preformed, and this making of a new determination, albeit pushed into the future, is the antithesis of preformation.

If pushed to its extreme conception of infinite encasement, then preformation is absurd; if not pushed to this extreme, preformation will not account for the determination of ultimate future generations; and if it did apply, preformation would be an unsatisfactory view in that it assumes that the diversity which is progressively manifested in development is ready-made at the start, and in no way attempts to explain it causally or to interpret it in simpler terms.

§ 2

Logically, the preformationist view is associated with the notion of separate particles being transmitted from parent to offspring, though the converse does not hold. In preformationist theory, the hypothetical particles establish the one-to-one link between the corresponding organs and parts of parent and offspring, whereas the modern view, which combines an epigenetic outlook on development with the particulate theories of neo-Mendelism, denies any such simple correspondence between hereditary germinal unit and developed adult character. Darwin's theory of pangenesis resembles that of the Hippocratic writer in this respect, the pangens being supposed to come from all parts of the body of the parent and to be transmitted, via the germ-cells or "semen", to the offspring whose development they mould. Embryologically, however, Darwin's theory is vague, and leaves the question of preformation open. Weismann's theory of the germ-plasm, in which the *determinants* are regarded as representing the predetermined but not spatially preformed diversity of the future embryo, differs from that of previous preformationists in that the particles are regarded as coming, *not* from the corresponding parts of the body of the parent, but from the germ-plasm, of which each generation of individual organisms is held to be nothing but the life-custodian. Weismann identified the determinants with the material in the nuclei of the cells, which material he (wrongly) supposed was divided unequally in the process of division or cleavage of the egg, so as to form a mosaic, the pieces (cells or regions) of which would then contain different determinants and would therefore be predetermined to develop in their respective different and definite directions.

According to the writer of the Hippocratic treatise *Peri Gones* and to Darwin, therefore, offspring resembles parent because the particles responsible for the development of the parts of the offspring come from the corresponding parts of the parent. According to Weismann, however, offspring resembles parent because both have derived similar particles (determinants) from a common source—the germ-plasm.

The question of the *origin* of the particles or hereditary factors and of their *distribution* from the parent to the offspring is one which principally concerns the science of genetics. The modern tendency is to accept the principle of a germ-plasm while recognising that it is not as inaccessible to the modifying action of external factors as Weismann contended. The question of the *function* of the particles or factors in converting the fertilised egg into the body of the adult is the concern of that modern and rather special branch of embryology usually called physiological genetics.

Before dealing with the conclusion derived directly from experimental work, a moment's attention may be turned to philosophical criticisms of the preformationist view that particles, determinants, or any hereditarily transmitted units or factors, can "explain" development. First of all, Aristotle pointed out that certain features in which offspring resembled parent could not be ascribed to the transmission of particles from corresponding parts, for the latter might be dead structures like nails or hair from which no particles could be expected to come, or again they might be such characters as timbre of voice or method of gait. He goes on to say, by way of illustration, that if a son resembles his father, the shoes he wears will be like his father's shoes, yet there can, of course, be no question of particles here. In other cases, resemblance may refer to structure, plan or configuration rather than to the material of which it is composed, and it is hard to see how particles can represent such structure, plan or configuration. Again, how is the eventual beard of a son to be explained if he was born to a beardless father? To these objections might be added the insuperable difficulty of accounting for the production of offspring structurally different from the parent, as when the egg laid by a queen bee develops into a worker, or, even more generally, when a mother bears a son or a man fathers a daughter.

If, then, particles coming from corresponding parts are not required in some cases and cannot be resorted to in others in order to explain development and hereditary resemblance, why should they be postulated in any case? This, of course, concerns genetics as much as embryology, but Aristotle came very close to the crucial problem of the latter when he wrote: "either all the parts, as heart, lung, liver, eye, and all the rest, come into being together, or in succession....That the former is not the fact is plain even to the senses, for some of the parts are clearly visible as already existing in the embryo while others are not; that it is not because of their being too small that they are not visible is clear, for the lung is of greater size than the heart, and yet appears later than the heart in the original development".[1]

Simple observation, therefore, had even in Aristotle's time given the lie direct to the view that the embryo is a spatially preformed miniature adult. Similar but more exhaustive and more crucial observational evidence against the preformationist view was supplied by William Harvey (who referred to development as "*epigenesin sive partium superadditionem*") and, notably, by Caspar Friedrich Wolff. The conclusion to which the latter came is the same as that of Aristotle. In the earliest stages of the development of the fowl, the microscope reveals the presence of little globules heaped together without coherence, and a miniature of the adult simply does not exist. Further, no refuge can be taken in the assumption that the miniature is too small to be seen, for its parts (globules) are clearly visible, and, *a fortiori*, therefore, the whole. The plain fact is that the miniature of the adult is not there.

The necessary epigenetic correlate of this fact has been admirably put by Delage in the following words: "latent or potential characters are absent characters....The egg contains nothing beyond the special physico-chemical constitution that confers upon it its individual properties *qua* cell. It is evident that this constitution is the condition of future characters, but this condition is in the egg extremely incomplete, and to say that it is complete but latent is to falsify the state of affairs. What is lacking to complete the conditions does not exist in the egg in a state of inhibition, but outside the egg altogether, and can equally well occur or not occur at the required moment. Ontogeny is *not* completely determined in the egg".[1] We might sum up the position by saying that to maintain the full preformationist view would partake of the nature of fraudulent book-keeping.

There is no way of saving the view that the adult is preformed in the egg as a diminutive replica. The more subtle idea of Bonnet's, of preformed "organic points", or of determinants unequally distributed between the cells into which the egg divides, also met its doom a century ago, when Etienne Geoffroy St Hilaire (1826) experi-

[1] Quoted from Russell, *loc. cit.*

mentally produced developmental monsters out of chick embryos, and rightly concluded that since there cannot have been any preformation of these experimentally induced monstrosities, normal embryos need not be preformed either. A better known death-knell for the preformationist hypothesis is Driesch's demonstration that in many forms, the parts (blastomeres or groups of blastomeres) of the dividing egg could, if separated, develop into complete little embryos. It is impossible to imagine any theory of preformation, however elastic, which will explain the fact that an egg normally develops into a single embryo, and yet can be made to give rise to two or four whole embryos.

§ 3

The inevitable conclusion is that development involves a true increase of diversity, a creation of differentiation where previously none existed, and that the interpretation of embryonic development must be sought along the lines of some epigenetic theory. The problem is narrowed down to a search for a principle on which it is possible to understand how the determinations of the future embryo can arise out of a non-diversified egg. It is the great merit of C. M. Child to have shown in theory how this is possible. Briefly, his view (which will be considered in detail later) is that certain external factors set up quantitative differentials in the egg and embryo, as a result of which qualitative differences of structure ultimately ensue. The egg contains a complex of inherent factors, notably the genes of Mendelian theory, which have been transmitted from its parents and ensure that it shall develop in a specific fashion, and that if the environment is normal it shall develop so as to resemble other members of its kind. However, these internal inherent and transmitted factors of the egg, though genetically preformed, cannot be regarded as a preformation in a spatial or embryological sense. What they do is to confer upon the developing organism the capacity to respond in a specific way to certain stimuli which in the first instance are external to the organism. It is, as Ray Lankester and Herbst first suggested, these responses of a specific hereditary outfit to stimuli outside themselves, which constitute development.

Differentiation is evoked out of the egg afresh in each and every generation: every individual organism is created by epigenesis during its own life-history. The environment is as important as are the internal and transmitted hereditary factors, and both must be normal for a normal embryo to be developed. If the environment is abnormal, there will either be no development at all, or an abnormal and abortive development, and the same fate befalls an abnormal hereditary constitution reacting with a normal environment. If both the environmental and hereditary factors are within the bounds of normality, then development will follow the lines which are characteristic for the particular species of organism in question.

The origin of differentiation and of the epigenetic process are therefore to be found in the processes by which in the first place quantitative differentials are induced in the egg by external factors, and in the second place qualitative structural diversities result from the interaction of the quantitative differentials with the inherited constitution. It is these problems which form the subject-matter of this book.

§ 4

Meanwhile, it is necessary to pause, and to consider for a moment how the causal postulate can be applied to development conceived as an epigenesis. On the preformationist view, the causes of development present no particular difficulty, for differentiation is then supposed to be there all the time and to require nothing but expansion or unrolling ("evolution" in the eighteenth-century sense) in order to become visible. Even after the discomfiture of the preformationist view at the hands of Wolff and others, and the acceptance in principle of an epigenetic theory of development, the need for an application of the causal postulate was cloaked by the unfortunate effects of Haeckel's theory of recapitulation. This view, pushed to its ultimate conclusion, maintained that ontogeny or embryonic development was inevitably a recapitulation of phylogeny or racial evolutionary history, and that phylogeny was the mechanical cause of ontogeny, whatever Haeckel may have meant by such a statement. If this was true, then clearly there was no need to look for other causes than the evolutionary history in order to explain development. But, as Wilhelm His saw, it was not true.

The Aristotelian view of the causes of epigenesis is complicated and somewhat grotesque from the modern point of view, but it introduces some notions which are very apposite in any discussion of this problem. First of all, Aristotle realised the principle of linked causes, which may be illustrated with reference to the interdependence of meshed cogwheels in machinery. He wrote: "that which made the semen sets up the movement in the embryo, and makes the parts of it by having first touched something, though not continuing to touch it".[1] This is the principle on which a clock works after it has been wound up, and many thinkers have imagined development as the working of machinery originally wound up and set going at conception, the continued working of which was due to the progressive assumption of causal activity by the results of previous causes.

But Aristotle did not regard this view as providing a sufficient explanation; in addition, he held that the "soul" was active in controlling the material forces and mechanical processes of development. Kindred views have been expressed by von Baer and by Driesch. The former held that each stage of development was a necessary *condition* for the production of the following stage, but was not in any full sense its *cause*, for in addition he regarded the "essential nature" of the parent as responsible for controlling the development of the offspring. Driesch has adapted Aristotle's view of the functions of the "soul" in his theory of entelechies.

On the other hand, Wilhelm His, having overthrown Haeckel's theory of recapitulation, regarded each stage of development as a sufficient cause of the following stage, and so paved the way for a new branch of science: Entwicklungsmechanik or causal embryology, the foundations of which were laid by Wilhelm Roux. In what may be regarded as the "charter" of the new science, Roux prescribes the analysis of development into so-called complex components, such as assimilation, growth, cell-division, etc. Ultimately he supposed these complex components to be reducible to simple components, which in turn would be capable of interpretation in terms of physics and chemistry (Roux, 1885).

Whether future research will succeed in so reducing the complex components of development as to render them susceptible of ex-

[1] Quoted from Russell, *loc. cit.*

pression in fundamental physico-chemical terms is a question of its own, and one which has been much obscured by the introduction of what are ambiguously called "mechanistic" explanations. As Woodger's (1928) analysis has shown, the term "mechanistic" as applied to biological phenomena may mean: either

1. That the structure and function of living organisms is to be completely explained in terms of "little bits of stuff pushing one another about" in accordance with the classical laws of mechanics; or
2. That all the phenomena presented by a living organism are ultimately capable of analysis in terms of the laws of physics and chemistry; or
3. That a living organism is in some sense analogous to a human-made machine and that its processes are explicable in terms of this analogy; or
4. That the causal postulate is perfectly applicable to living organisms and can be satisfactorily applied to the biological order of things, whether or no the phenomena of the biological order can ultimately be brought into line with physico-chemical phenomena and prove susceptible of analysis in physico-chemical terms.

The fourth of these alternatives is generally accepted, and, indeed, the whole science of causal embryology is based upon it. The second alternative is also widely accepted, and is the only fruitful working hypothesis for the biologist. It is clear, however, that it may require modification, for further study, notably of the phenomena of life, is likely to reveal new and hitherto unsuspected physico-chemical properties of matter. Accordingly, it is necessary to take physics and chemistry in the most extended sense. The advances made in physics itself have rendered the first alternative untenable, and the third cannot pretend to have more value than can ever be ascribed to processes of reasoning by analogy; thus, what may be called the cruder mechanistic view embodied in alternatives 1 and 3 may be excluded.